

Appl. No. 09/426,791  
 Amendment dated April 8, 2005  
 Reply of Office Action dated October 20, 2004

# **REMARKS**

Claims 1, 6, 49, and 52-54 are amended. Claims 5, 7-14, 17-49, and 52 are cancelled.  
 Claims 1-4, 6, 15, 16, 50, 51, 53, and 54 are currently pending.

## **I. Rejection Under 35 U.S.C. § 103(a)-Obviousness**

Claims 1-4, 6, 13-16, and 49-54 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Goldstein *et al.* (Journal of Cardiovascular Pharmacology, 22:253-258 (1993) in view of Kataria *et al.* (J. Cardiothoracic Anesth., Suppl. 2:13-16 (1990)).

Applicant respectfully traverses the above rejection as the teachings of Goldstein *et al.* and Kataria *et al.*, taken alone or in combination, do not teach or suggest the presently claimed method.

Applicant's invention is drawn, in part, to the surprising discovery that administration of  $\beta_1$ -adrenergic selective blockers *immediately after surgery and daily thereafter* reduces cardiovascular complications after surgery. While not wishing to be bound by any particular theory, it is believed that intensive administration of  $\beta_1$ -adrenergic selective blockers during this important period of "immediately after surgery" imparts increased survival and reduces cardiovascular complications in patients undergoing surgical stress.<sup>1</sup> As corroborated by Dr. Dennis Mangano's declaration under Rule 132 filed herewith, these beneficial cardiovascular effects are realized when  $\beta_1$ -adrenergic selective blockers are administered to a patient *prior to emergence from anesthesia following surgery*. Mangano Declaration, at Paragraph 11.

Dr. Dennis Mangano's declaration filed herewith states that, at the time of filing, he understood the phrase administration "immediately after surgery" to mean that administration occurs prior to a patient's emergence from anesthesia following surgery. Mangano Declaration, at Paragraph 16. Moreover, Dr. Mangano further states that one of ordinary skill in the art would concur with his understanding of the phrase "immediately after surgery." Mangano Declaration, at Paragraph 13. Thus, the present invention is drawn, in part, to methods of reducing cardiovascular

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<sup>1</sup> Applicants Response of July 5, 2001 at pages 7-8

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disease complications by administering a near maximum effective dose of  $\beta_1$ -adrenergic selective blockers prior to a patient's emergence from anesthesia following surgery.

As amended herein, independent claims 1, 49, and 52 are drawn to methods of reducing cardiovascular complications comprising administering a  $\beta_1$ -adrenergic selective blocking agent *immediately after surgery and daily thereafter* until symptoms of cardiovascular stress are reduced.

"To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." See MPEP 2143.03 citing *In re Royka*, 490 F.2d 981.

According to Goldstein *et al.*, "[t]reatment with study medication [atenolol or nebivolol] was started 2 h after extubation by administration of 1 tablet daily of either 5 mg nebivolol or 50 mg atenolol and was continued for 10 days." Goldstein *et al.*, page 254, column 2, paragraph 1 (emphasis added). As Goldstein *et al.* teaches that study medication is administered by tablets, it can be deduced that Goldstein *et al.* teaches administering atenolol or nebivolol after surgery, after the patient has emerged from anesthesia, and not before a patient emerges from anesthesia (i.e., immediately after surgery), as is presently claimed.

Thus, Goldstein *et al.* does not teach or suggest the presently claimed methods because the reference does not teach or suggest administering a  $\beta_1$ -adrenergic selective blocking agent prior to emergence from anesthesia, immediately after surgery and daily thereafter.

Furthermore, Goldstein *et al.* does not teach or suggest administering a near maximum effective dose of atenolol, as is recited in the present claims. According to Goldstein *et al.* patients were administered "1 tablet daily of either 5 mg nebivolol or 50 mg atenolol." Goldstein *et al.*, page 254, column 2, paragraph 1. The near maximum effective dose of atenolol is, on average about 2 mg/kg.<sup>2</sup> Accordingly, the near maximum effective dose of atenolol for patients weighing 78 kg is, on average, 156 mg. Therefore, the dosage in Goldstein *et al.* is less than one-third of the average maximum effective dose proscribed for atenolol. Goldstein *et al.* fails to teach or suggest

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<sup>2</sup> See Response of July 5, 2001 at page 9, Paragraph 3 citing Physician's Desk Reference (2001).

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administration of a near maximum effective dose of a  $\beta_1$ -adrenergic selective blocker and as such teaches away from the instantly claimed invention.

Kataria *et al.* has been cited for allegedly teaching the administration of esmolol "intraoperatively and immediately after general surgery, during emergence from anesthesia." See Office Action, page 2, paragraph 6 - page 3, paragraph 1 (emphasis added).

Applicant respectfully traverses the above rejection as Kataria *et al.* does not teach or suggest administration of a  $\beta_1$ -adrenergic selective blocker immediately after surgery i.e., prior to a patient's emergence from anesthesia. According to Kataria *et al.* "[i]f, on emergence from anesthesia in the operating room or in the recovery room, the patient developed a systolic blood pressure (SBP) of  $\geq$ mm Hg or diastolic blood pressure (DBP) of  $\geq$ mm Hg with a heart rate (HR)  $\geq$ 70 beats / min for at least 5 minutes . . . esmolol was administered." See Kataria *et al.* page 13, Col. 2, Par. 1 (emphasis added). Thus, while Kataria *et al.* discloses administration of esmolol "on emergence from anesthesia," it does not teach administration of a beta-blocker prior to emergence from anesthesia.

For the foregoing reasons, Applicants respectfully submit that the reference does not teach or suggest the administration of a  $\beta_1$ -adrenergic selective blocker immediately after surgery, as is recited in the present claims.

Moreover, as neither Goldstein *et al.* nor Kataria *et al.*, taken alone or in combination, teach or suggest administration of a near maximum effective dose of a  $\beta_1$ -adrenergic selective blocking agent immediately after surgery and daily thereafter, Applicants respectfully request that the above rejection of claims 1-4, 6, 13-16, and 49-54 be withdrawn.

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**CONCLUSION**

Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

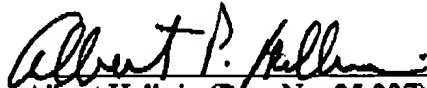
The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 27116-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

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By:



Albert Halluin (Reg. No. 25,227)  
Maya Skubatch (Reg. No. 52,505)

650 Page Mill Road  
Palo Alto, CA 94304  
Direct Dial: (858) 350-2365  
Customer No. 021971